Summary
Host-pathogen interactions are emerging as a significant field in science that deals with balance of host defenses and pathogen virulence mechanisms. Studying host-pathogen interactions can unravel the molecular, cellular and population level mechanism from both the host and pathogen perspective. Infectious diseases have revolutionized rapidly in the recent past causing major health problem and have been the reason for millions of deaths worldwide. The Gram positive *Staphylococcal* spp. causes a range of illnesses from minor skin infections, such as pimples, impetigo, boils, cellulitis, folliculitis, carbuncles, scalded skin syndrome and abscesses, to life-threatening diseases such as pneumonia, meningitis, osteomyelitis, endocarditis, TSS, bacteremia and sepsis. Of note, the pathogen has devised cleverly to circumvent the damage instigated by the innate immune system. *S. aureus* has an extraordinary array of virulence factors that allows it to persist during odd conditions within the human host. This makes the mankind difficult to become vulnerable to *S. aureus* infections. On the other hand, the opportunistic *P. mirabilis* is widely distributed in the natural environment. During favorable conditions they can cause severe infections in immuno-compromized people. The impact of *P. mirabilis* in a host system has been a topic that was excluded at many instances. The upheaval of nosocomial infection diverted the researchers to quarantine it as a separate area of research interest.

There have been a number of models to study the host-pathogen interactions such as yeast, worm and fly. The nematode *Caenorhabditis elegans* has outshined as a facile and economical model host for the study of the evolutionarily conserved mechanism of microbial pathogenesis and innate immunity. Using this live animal model as a platform for detecting the mechanisms involved in protecting the host at gene and protein level aids in validating the target molecule for drug discovery. With the awareness rising on the emergence of new strains and antibiotic resistance, *C. elegans* provides a powerful tool to dissect the mechanisms involved in host defenses.
Based on these specifics, the objectives of the present study were designed as follows:

- To explore the effects of externally induced heat shock in the longevity of *C. elegans* against *S. aureus* and *P. mirabilis* infections.
- To determine the presence of immunological memory in *C. elegans* during *S. aureus* and *P. mirabilis* exposures.
- To study the response and regulation of the host immune system during subsequent (*S. aureus* and *P. mirabilis*) infections through proteomic approaches.
- To analyze the physiological and molecular level changes at single worm level during *S. aureus* and *P. mirabilis* infections.

Temperature overwhelmingly influences aging in both poikilotherms and homeotherms. In the nematode *C. elegans*, alterations in a number of independent pathways, including the IIS pathway, are known to increase longevity and stress resistance. In the present study, *C. elegans*, a poikilothermic organism, was found to lengthen its lifespan with increased resistance against *S. aureus* when an external heat shock is applied for a short period. The same effect was analyzed with the long lived *daf-2* mutants which is a key regulator of IIS pathway. While, the chemotaxis assay performed with wild type N2 exhibited an aversion to *S. aureus* and attraction towards *P. mirabilis*, suggesting that, heat induction did not affect the choice preference of the nematode. Molecular studies suggested that HSF-1 was required for IIS to modulate longevity while the HSPs which is under the control of HSF-1 helps in chaperonic activity and regulates certain set of genes needed for pathogen resistance and longevity. It was also found that SGK-1 mediates the signal between IIS pathway and heat shock pathway which subsequently induced pathogen resistance and also extended the lifespan.
Storage of memory is an important attribute to react to the state of environment a host system is present in. Given the prominence of memory storage, the capacity of the host to store the information after a definite period of training was assessed. Depending upon the information learned and the rehearsals given the duration of memory stored is determined. While the basic functioning of the nervous system of *C. elegans* has been extensively studied, its behavioural plasticities have not been fully reconnoitered because of the limited availability of assay systems. In *C. elegans*, reduced access to food requires both changes in behavior as well as metabolic adaptation for survival. CREB transcription factor which plays a crucial role in memory has a homolog in *C. elegans*, *crh-1*. *crh-1* appears to influence memory processes to certain extent by habituation of the host to a particular environment. The discrimination between the pathogen and a non-pathogen is essential for *C. elegans* in a microbial niche to determine its survival. However, training the nematodes in the presence of a virulent pathogen (*S. aureus*) and an opportunistic pathogen (*P. mirabilis*) separately exhibits a different behavioural paradigm. Following habituation of the nematodes to *S. aureus* and *P. mirabilis*, the wild type nematodes exhibited a positive response towards the respective pathogen which diminished slowly after 2 h. In contrary to the wild type, the *crh-1* deficient nematodes had a defective memory post habituation. The molecular data also reinforces the importance of *crh-1* gene in retaining the memory of nematode. Further, the presence of neurotransmitters such as dopamine and octapamine help in sustenance of the memory. Disturbing these neurotransmitters with a carbamate molecule diminishes the memory storage ability of nematode.

With a wide range of bacterial infections growing, it has become a big challenge to the research field to combat the newly emerging diseases. Immuno-compromised patients are vulnerable to opportunistic infections. The effect of opportunism was studied with the help of *C. elegans*. *P. mirabilis*, an opportunistic pathogen infects the nematode when the immune
system is compromised. In the present study, the *C. elegans* was pre-exposed to *S. aureus* for a short term, and then consecutively infected with *P. mirabilis*. The primary infection caused by *S. aureus* makes the immune system of *C. elegans* vulnerable making it easy for *P. mirabilis* to colonize efficiently during subsequent exposure, thereby stimulating the immune system of the nematode. In this study, the *C. elegans* exposed to the pathogens (*S. aureus* 4 h/ *P. mirabilis* 40 h and *S. aureus* 8 h/ *P. mirabilis* 60 h time points) showed a substantial differences in the banding patterns of SDS-PAGE gel, when compared to their respective OP50 fed controls. 2-DE identified a total of 235 proteins from all the time points which had >1.5 fold regulation. The regulated protein spots were identified by MALDI-TOF-TOF analysis and one common protein CDC-25.1 was found to be regulated in all the comparative time points. CDC-25.1 was seemed to down regulate during subsequent infection and up regulate in single infection. The transcriptomic regulation of *cdc-25.1* also reflects the protein regulation. The quantification of intestinal colonization also supports the hypothesis comprehending the infectious nature of *P. mirabilis* after *S. aureus* infection. In addition to it, survival assay in *cdc-25.1* mutant nematodes confirm the susceptibility of host during subsequent infection.

Though the idea of cumulative effect of immune regulation from a group of *C. elegans* was established with various bacterial pathogens, the individual response given by the nematode is still an enigmatic issue. The killing of individual nematode seems to be early during *S. aureus* exposure. The passage of pathogen entry was determined and visualized that *S. aureus* enters through pharyngeal region and *P. mirabilis* choses either anal or vulval opening. The virulence nature of the pathogens was determined through FTIR and CV indicates that *S. aureus* showed significant difference than *P. mirabilis* and *E. coli* OP50. Concomitantly, the vertical transfer of bacterial colonies in the from parent to the progeny’s intestine confirms the pathogenicity of *S. aureus* which was not observed in case of *P.*
*mirabilis*. Single worm proteomic studies also articulate the presence of proteins that play a significant role in innate immunity.

Altogether, the current study provides an important insight into the innate immune regulation of *C. elegans* against *S. aureus* and *P. mirabilis* at different perceptions like external heat induced longevity, memory capacity, regulation during subsequent infection and single worm studies. The present study has advanced our knowledge on host-pathogen interactions in a more descriptive manner. Thus, *C. elegans* provides a perfect platform to decipher more gene/protein targets to boost the immunity.